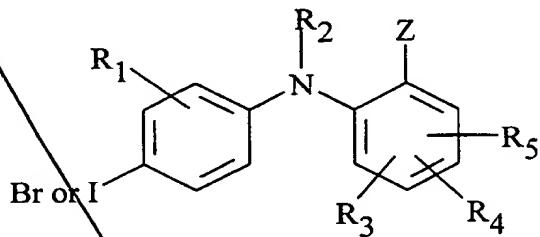


CLAIMS

What is claimed is:

- 5
- Subj 1*
- 10
- 15
- 20
- Subj 2*
- 25
1. A method for treating or preventing arthritis in a mammal, said method comprising the step of administering to a patient suffering from arthritis and in need of treatment, or to a patient suspected of developing arthritis, an effective antiarthritic amount of a MEK inhibitor.
 2. The method according to Claim 1 wherein the arthritis is rheumatoid arthritis or osteoarthritis.
 3. The method according to Claim 2, wherein the arthritis is osteoarthritis.
 4. The method according to Claim 2, wherein the arthritis is rheumatoid arthritis.
 5. The method according to Claim 1, wherein said MEK inhibitor is a selective MEK1 or MEK 2 inhibitor.
 6. The method according to Claim 1 wherein the MEK inhibitor is a compound of Formula I



I

wherein:

R₁ is hydrogen, hydroxy, C₁-C₈ alkyl, C₁-C₈ alkoxy, halo, trifluoromethyl, or CN;

R₂ is hydrogen;

25

R₃, R₄, and R₅ independently are hydrogen, hydroxy, halo, trifluoromethyl, C₁-C₈ alkyl, C₁-C₈ alkoxy, nitro, CN, or -(O or NH)_m-(CH₂)_n-R₉, where R₉ is hydrogen, hydroxy, COOH, or NR₁₀R₁₁;

5 n is 0-4;

m is 0 or 1;

A2
Cont
R₁₀ and R₁₁ independently are hydrogen or C₁-C₈ alkyl, or taken together with the nitrogen to which they are attached can complete a 3-10 member cyclic ring optionally containing 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N-C₁-C₈ alkyl;

10 Z is COOR₇, tetrazolyl, CONR₆R₇, CONHNR₁₀R₁₁, or CH₂OR₇;

R₆ and R₇ independently are hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl,

C₂-C₈ alkynyl, (CO)-C₁-C₈ alkyl, aryl, heteroaryl, C₃-C₁₀ cycloalkyl, or

15 C₃-C₁₀ (cycloalkyl optionally containing one, two, or three heteroatoms selected from O, S, NH, or N alkyl); or R₆ and R₇ together with the nitrogen to which they are attached complete a 3-10 member cyclic ring optionally containing 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N alkyl; and wherein any of the foregoing alkyl, alkenyl, aryl, heterocyclic, and alkynyl groups can be unsubstituted or substituted by halo, hydroxy, C₁-C₆ alkoxy, amino, nitro, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, C₃-C₆ cycloalkyl, phenyl, phenoxy, C₃-C₅ heteroaryl, or C₃-C₅ heteroaryloxy;
20 or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof.

25 7. The method according to Claim 6 wherein the MEK inhibitor is a compound selected from:

[4-Chloro-2-(1H-tetrazol-5-yl)-phenyl-(4-iodo-2-methyl-phenyl)-amine;

(4-iodo-2-methyl-phenyl)-[2-(1H-tetrazol-5-yl)-phenyl]amine;

Part B
Cont

[4-nitro-2-(1H-tetrazol-5-yl)-phenyl-(4-iodo-2-methyl-phenyl)-amine;

5
4-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid;
3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;
3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;
5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

10
5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;
Sodium 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoate;
5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;
2-(4-Iodo-2-methyl-phenylamino)-5-nitro-benzoic acid;
4-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;
2-(4-Iodo-2-methyl-phenylamino)-benzoic acid;
5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;
5-Iodo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;
2,3,5-Trifluoro-4-(4-iodo-2-methyl-phenylamino)-benzoic acid;
2-(4-Iodo-phenylamino)-5-methoxy-benzoic acid;
5-Methyl-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;
2-(4-Iodo-2-methyl-phenylamino)-4-nitro-benzoic acid;
2-(4-Bromo-2-methyl-phenylamino)-4-fluoro-benzoic acid;
2-(2-Bromo-4-iodo-phenylamino)-5-nitro-benzoic acid;
2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-benzoic acid;
5-Chloro-N-(2-hydroxyethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

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benzamide;
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-benzamide;
N-Ethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide;

25
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1H-tetrazol-5-yl)-benzamide;

30
5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

- 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide;
[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoylamino]-acetic acid;
- 5
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-propyl-benzamide;
5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
N,N-Diethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
10
4-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)-benzamide;
N,N-Diethyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;
N-Butyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
5-Chloro-N,N-diethyl-2-(4-ido-2-methyl-phenylamino)-benzamide;
5-Bromo-2-(4-ido-2-methyl-phenylamino)-N,N-dimethyl-benzamide;
5-Bromo-3,4-difluoro-N-(2-hydroxy-ethyl)-2-(4-ido-2-methyl-phenylamino)-benzamide;
- 20
N-(2,3-Dihydroxy-propyl)-3,4-difluoro-2-(4-ido-2-methyl-phenylamino)-benzamide;
5-Bromo-3,4-difluoro-2-(4-ido-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;
3,4-Difluoro-N-(2-hydroxy-ethyl)-2-(4-ido-2-methyl-phenylamino)-benzamide;
- 25
N-(2,3-Dihydroxy-propyl)-4-fluoro-2-(4-ido-2-methyl-phenylamino)-benzamide;
3,4-Difluoro-N-(3-hydroxy-propyl)-2-(4-ido-2-methyl-phenylamino)-benzamide;
- 30
5-Bromo-3,4-difluoro-2-(4-ido-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
5-Bromo-3,4-difluoro-2-(4-ido-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide;

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Part B
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- 4-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Bromo-N-(3-dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5
5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;
- 10
3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide;
- 15
N-(3-Dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- N-Benzyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethyl)-benzamide;
- 20
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;
- 25
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thiophen-2-yl-ethyl)-benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
- 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-morpholin-4-yl-ethyl)-benzamide;
- 30
5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;

- 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;
- (3-Hydroxy-pyrrolidin-1-yl)-[2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-methanone;
- 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
- 5-Bromo-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide;
- N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-chloro-2-(4-iodo-2-methyl- phenylamino)- benzamide;
- N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-bromo-2-(4-iodo-2-methyl- phenylamino)- benzamide;
- N-{3-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)- benzamide;
- 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl- benzamide;
- 5-Bromo-2-(4-iodo-2-ethyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
- 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;
- 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
- 5-Chloro-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-fluoro-2-(4-iodo-2-methyl- phenylamino)- benzamide;
- 5-Chloro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Chloro-N-(3-diethylamino-2-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

Sub B
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5-Bromo-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

5 N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-2-(4-iodo-2-methyl-phenylamino)-5-nitro- benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

10 5-Chloro-N-(3-diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

15 2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(2-piperidin-1-yl-ethyl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperazin-1-yl-ethyl)-benzamide;

20 N-(2-Diethylamino-ethyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

25 N-(3-Hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

5-Fluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

30 N-(3-Diethylamino-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(3-Diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

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- 2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(3-piperidin-1-yl-propyl)-benzamide;
- [5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-(3-hydroxy-pyrrolidin-1-yl)-methanone;
- 5-Bromo-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;
- 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;
- [5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;
- N-(3-Diethylamino-2-hydroxy-propyl)-5-fluoro-2-(4-ido-2-methyl-phenylamino)- benzamide;
- N-Cyclopropyl-5-fluoro-2-(4-ido-2-methyl-phenylamino)-benzamide;
- 5-Chloro-N-(2-hydroxy-ethyl)-2-(4-ido-2-methyl-phenylamino)-benzamide;
- 5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-ido-2-methyl-phenylamino)-benzamide;
- N-Benzyl-5-fluoro-2-(4-ido-2-methyl-phenylamino)-benzamide;
- N-Benzyl-5-bromo-2-(4-ido-2-methyl-phenylamino)-benzamide;
- 2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide;
- 5-Bromo-N-(2-hydroxy-ethyl)-2-(4-ido-2-methyl-phenylamino)-benzamide;
- N-(2-Hydroxy-ethyl)-5-iodo-2-(4-ido-2-methyl-phenylamino)-benzamide;
- N-(2-Hydroxy-ethyl)-2-(4-ido-2-ethyl-phenylamino)-5-nitro-benzamide;

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- 2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-
benzamide;
- 5-Chloro-N-cyclopropyl-2-(4-ido-2-methyl-phenylamino)-
benzamide;
- 5-Fluoro-2-(4-ido-2-methyl-phenylamino)-N-methyl-N-phenyl-
benzamide;
- N-Allyl-5-fluoro-2-(4-ido-2-methyl-phenylamino)-benzamide;
- N-Benzyl-5-iodo-2-(4-ido-2-methyl-phenylamino)-
benzamide;
- 5-Fluoro-2-(4-ido-2-methyl-phenylamino)-N-(4-sulfamoyl-
benzyl)-benzamide;
- N-Allyl-5-chloro-2-(4-ido-2-methyl-phenylamino)-benzamide;
- N-Cyclopropyl-2-(4-ido-2-methyl-phenylamino)-5-nitro-
benzamide;
- 5-Bromo-N-cyclopropyl-2-(4-ido-2-methyl-phenylamino)-
benzamide;
- 5-Chloro-2-(4-ido-2-methyl-phenylamino)-N-methyl-N-phenyl-
benzamide;
- 5-Iodo-2-(4-ido-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-
benzamide;
- 5-Bromo-2-(4-ido-2-methyl-phenylamino)-N-(4-sulfamoyl-
benzyl)-benzamide;
- N-Allyl-2-(4-ido-2-methyl-phenylamino)-5-nitro-benzamide;
- 2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-
benzamide;
- N-Allyl-5-bromo-2-(4-ido-2-methyl-phenylamino)-benzamide;
- 5-Fluoro-2-(4-ido-2-methyl-phenylamino)-N-(3-methyl-benzyl)-
benzamide;
- N-Cyclopropyl-5-iodo-2-(4-ido-2-methyl-phenylamino)-
benzamide;
- 5-Bromo-2-(4-ido-2-methyl-phenylamino)-N-methyl-N-phenyl-
benzamide;

Sub B
cont

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- N-Benzyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-
benzamide;
- N-Cyclohexyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-
benzamide;
- 5 N-Allyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-
benzamide;
- 2-(4-Iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-5-nitro-
benzamide;
- 10 5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-
benzamide;
- N-Cyclohexyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-
benzamide;
- 5-Chloro-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-
benzamide;
- 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-
benzamide;
- 5-Bromo-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-
benzamide;
- 20 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-
benzamide;
- N-Cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-
benzamide;
- N-Benzyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-
benzamide;
- 25 N-Benzyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-
benzamide;
- 5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-
benzamide;
- 30 5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-
benzamide;
- 2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-
benzamide;

Sheet B
Cont

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5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenylbenzamide;

5
N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenylbenzamide;

10 N-(2-Hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

20 N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

25 N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenylbenzamide;

30 N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzyl alcohol;

[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol;

[2-(4-Iodo-2-methyl-phenylamino)-5-nitro-phenyl]-methanol;

Cont'd
B1
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*Part B
Cont*

and

[5-Bromo-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol;

N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide.

8. *SCS* *123* The method of claim 6, wherein the MEK inhibitor is a compound of Formula (I) wherein (a) R₁ is hydrogen, methyl, methoxy, fluoro, chloro, or bromo; (b) R₂ is hydrogen; (c) R₃, R₄, and R₅ independently are hydrogen, fluoro, chloro, bromo, iodo, methyl, methoxy, or nitro; (d) R₁₀ and R₁₁ independently are hydrogen or methyl; (e) Z is COOR₇, tetrazolyl, CONR₆R₇, CONHNR₁₀R₁₁, or CH₂OR₇; R₆ and R₇ independently are hydrogen, C₁₋₄ alkyl, heteroaryl, or C₃₋₅ cycloalkyl optionally containing one or two heteroatoms selected from O, S, or NH; or R₆ and R₇ together with the nitrogen to which they are attached complete a 5-6 member cyclic ring optionally containing 1 or 2 additional heteroatoms selected from O, NH or N-alkyl; and wherein any of the foregoing alkyl or aryl groups can be unsubstituted or substituted by halo, hydroxy, methoxy, ethoxy, or heteroaryloxy; (f) Z is COOR₇; (g) R₇ is H, pentafluorophenyl, or tetrazolyl; (h) R₃, R₄, and R₅ are independently H, fluoro, or chloro; (i) R₄ is fluoro; (j) two of R₃, R₄, and R₅ are fluoro; or (k) or combinations of the above.

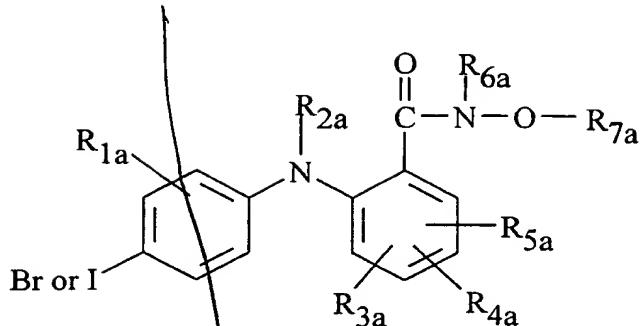
9. The method of claim 8, wherein the MEK inhibitor is a compound of Formula (I) wherein: Z is COOR₇; R₇ is H, pentafluorophenyl, or tetrazolyl; R₃ and R₅ are independently H, fluoro, or chloro; and R₄ is fluoro.

10. The method of Claim 1 wherein the MEK inhibitor is a compound of Formula II

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*Part B
Cont*

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wherein:

R_{1a} is hydrogen, hydroxy, C₁-C₈ alkyl, C₁-C₈ alkoxy, halo, trifluoromethyl, or CN;

5

R_{2a} is hydrogen;

R_{3a}, R_{4a}, and R_{5a} independently are hydrogen, hydroxy, halo, trifluoromethyl, C₁-C₈ alkyl, C₁-C₈ alkoxy, nitro, CN, or (O or NH)_m-(CH₂)_n-R_{9a}, where R_{9a} is hydrogen, hydroxy, CO₂H or NR_{10a}R_{11a}.

10

n is 0-4;

m is 0 or 1;

R_{10a} and R_{11a} independently are hydrogen or C₁-C₈ alkyl, or taken together with the nitrogen to which they are attached can complete a 3- to 10-member cyclic ring optionally containing one, two, or three additional heteroatoms selected from O, S, NH, or N-C₁-C₈ alkyl;

15

R_{6a} is hydrogen, C₁-C₈ alkyl, (CO)-C₁-C₈ alkyl, aryl, aralkyl, or C₃-C₁₀ cycloalkyl;

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R_{7a} is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₁₀ (cycloalkyl or cyclalkyl optionally containing a heteroatom selected from O, S, or NR_{9a});

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and wherein any of the foregoing alkyl, alkenyl, aryl, heteroaryl, heterocyclic, and alkynyl groups can be unsubstituted or substituted by halo, hydroxy, C₁-C₆ alkoxy, amino, nitro, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, C₃-C₆ cycloalkyl, phenyl, phenoxy, C₃-C₅ heteroaryl or

heterocyclic radical, or C₃-C₅ heteroaryloxy or heterocyclic radical-oxy; or R_{6a} and R_{7a} taken together with the N to which they are attached can complete a 5- to 10-membered cyclic ring, optionally containing one, two, or three additional heteroatoms selected from O, S, or NR_{10a}R_{11a}; or a pharmaceutically acceptable salt, ester, amide or prodrug thereof.

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11. The method of Claim 10, comprising a MEK inhibitor having a structure of Formula (II) wherein: (a) R_{1a} is H, methyl, fluoro, or chloro; (b) R_{2a} is H; R_{3a}, R_{4a}, and R_{5a} are each H, Cl, nitro, or F; (c) R_{6a} is H; (d) R_{7a} is methyl, ethyl, 2-propenyl, propyl, butyl, pentyl, hexyl, cyclopropylmethyl, cyclobutyl, methyl, cyclopropylmethyl, or cyclopropylethyl; and (e) the 4' position is I, rather than Br.

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12. The method of claim 11, comprising a MEK inhibitor having a structure of Formula (II) wherein: R_{4a} is F at the 4 position, para to the CO-N-R_{6a}-OR_{7a} group and meta to the bridging nitrogen; at least one of R_{3a} and R_{5a} is F or Cl; and R_{1a} is methyl or chloro.

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13. The method of Claim 10, comprising a MEK inhibitor having a formula selected from:

- 4-Fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(methoxy)-benzamide;
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-nyloxy)-benzamide;
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-benzamide;
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-benzamide;
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-enyloxy)-benzamide;

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- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropylmethoxy)-benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopentoxy)-benzamide;
- 5 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-furylmethoxy)-benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-ethoxy-benzamide;
- 10 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-2-enyloxy)-benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropylmethoxy)-benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1-methylprop-2-nyloxy)-benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-phenylprop-2-nyloxy)-benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-5-phenylpent-2-en-4-nyloxy)-benzamide;
- 20 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-nyloxy)-benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(propoxy)-benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclobutyloxy)-benzamide;
- 25 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methyl-prop-2-enyloxy)-benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-benzamide;
- 30 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-3-ynyl-oxo)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopentyl-oxo)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-(2-fluorophenyl)-prop-2-ynyl-oxo)-benzamide;

5 5-Bromo-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

10 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(n-propoxy)-benzamide;

15 5-Bromo-3,4-difluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(but-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

15 5-Bromo-N-butoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-but-2-enyloxy)-benzamide;

20 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-pent-2-en-4-ynyl-oxo)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-benzyl)-N-[5-(3-methoxy-phenyl)-3-methyl-pent-2-en-4-ynyl-oxo]-benzamide;

25 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyl-oxo)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-[3-(3-methoxy-phenyl)-prop-2-ynyl-oxo]-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(thiopen-2-ylmethoxy)-benzamide;

30 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(pyridin-3-ylmethoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-(2-fluorophenyl)-prop-2-ynyl-oxo)-benzamide;

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- 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(ethoxy)-benzamide;
- 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropylmethoxy)-benzamide;
- 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(isopropoxy)-benzamide;
- 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-but-3-yloxy)-benzamide;
- 5-Chloro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(tetrahydro-pyran-2-yloxy)-benzamide;
- 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methoxy-benzamide;
- 4-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide;
- 5-Fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide;
- 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(tetrahydropyran-2-yloxy)-benzamide;
- 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-phenylprop-2-yloxy)-benzamide;
- 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-furylmethoxy)-benzamide;
- 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-benzamide;
- 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(but-3-yloxy)-benzamide;
- 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-methyl-prop-2-enyloxy)-benzamide;

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- 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(but-
2-enyloxy)-benzamide;
- 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(methoxy)-
benzamide;
- 5 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(ethoxy)-
benzamide;
- 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-
(cyclobutoxy)-benzamide;
- 10 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(isopropoxy)-
benzamide;
- 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-
(2-phenoxyethoxy)-benzamide;
- 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclopropyl-
methoxy)-benzamide;
- 15 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(n-propoxy)-
benzamide;
- 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(1-methyl-
prop-2-nyloxy)-benzamide;
- 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-
(3-(3-fluorophenyl)-prop-2-nyloxy)-benzamide;
- 20 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-
(4,4-dimethylpent-2-nyloxy)-benzamide;
- 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-
(cyclopentoxy)-benzamide;
- 25 3,4,5-Trifluoro-N-hydroxy-2-(4-ido-2-methyl-phenylamino)-
benzamide;
- 5-Chloro-3,4-difluoro-N-hydroxy-2-(4-ido-2-methyl-
phenylamino)-benzamide;
- 30 5-Bromo-3,4-difluoro-2-(2-fluoro-4-ido-phenylamino)-N-
hydroxy-benzamide;
- N-Hydroxy-2-(4-ido-2-methyl-phenylamino)-4-nitro-benzamide;
- 3,4,5-Trifluoro-2-(2-fluoro-4-ido-phenylamino)-N-hydroxy-
benzamide;

b6 b7C
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- 5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;
- 5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;
- 5
2-(2-Fluoro-4-iodo-phenylamino)-N-hydroxy-4-nitro-benzamide;
- 2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-hydroxy-benzamide;
- 5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;
- 10
5-Bromo-2-(2-bromo-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;
- 2-(2-Chloro-4-iodo-phenylamino)-N-hydroxy-4-methylbenzamide;
- 2-(2-Bromo-4-iodo-phenylamino)-3,4,5-trifluoro-N-hydroxy-benzamide;
- 15
2-(2-Bromo-4-iodo-phenylamino)-5-chloro-3,4-difluoro-N-hydroxy-benzamide;
- 2-(2-Bromo-4-iodo-phenylamino)-N-hydroxy-4-nitro-benzamide;
- 4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;
- 20
3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;
- 2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-hydroxy-benzamide;
- 2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;
- 25
2-(2-Bromo-4-iodo-phenylamino)-4-fluoro-N-hydroxy-benzamide;
- 2-(2-Bromo-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;
- N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(4-ido-2-methylphenylamino)-benzamide;
- 30
5-Chloro-N-cyclopropylmethoxy-3,4-difluoro-2-(4-ido-2-methylphenylamino)-benzamide;
- 5-Bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-benzamide;

b6 b7B
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N-Cyclopropylmethoxy-2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzamide;

5 N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

5-Chloro-N-cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide;

10 N-Cyclopropylmethoxy-2-(2-fluoro-4-iodo-phenylamino)-4-nitro-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide;

5-Bromo-2-(2-bromo-4-iodo-phenylamino)-N-ethoxy-3,4-difluoro-benzamide;

20 2-(2-Chloro-4-iodo-phenylamino)-N-ethoxy-4-nitro-benzamide;
2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-5-chloro-N-cyclopropylmethoxy-3,4-difluoro-benzamide

25 2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-nitro-benzamide;

N-Cyclopropylmethoxy-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

N-Cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

30 2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-fluoro-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-fluoro-benzamide; and

Sub B
15 Cont

Sub B1
Cont

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-
3,4-difluoro-benzamide

14. The method of claim 1, comprising a MEK inhibitor having a structure selected from:

5 2-(2-chloro-4-iodophenylamino)-5-chloro-N-cyclopropylmethoxy -3,4-difluorobenzamide (PD 297189); 2-(4-iodophenylamino)-N-cyclopropylmethoxy-5-chloro-3,4-difluorobenzamide (PD 297190); 2-(4-iodophenylamino)-5-chloro-3,4-difluorobenzoic acid (PD 296771); 2-(2-chloro-4-iodophenylamino)-5-chloro-3,4-difluorobenzoic acid (PD 296770); 5-chloro-3,4-difluoro-2-(4-ido-2-methylphenylamino)-benzoic acid (PD 296767); and 5-chloro-N-cyclopropylmethoxy -3,4-difluoro-2-(4-ido-2-methylphenylamino)-benzamide (PD _____).

- 10 15 15. A method of treating or preventing arthritis in a patient in need of treatment, or suspected of developing arthritis, said method comprising the step of administering an effective antiarthritic amount of a compound selected from:

20 20 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide (PD184352);
2-(2-Methyl-4-iodophenylamino)-N-hydroxy-4-fluorobenzamide (PD170611);
2-(2-Methyl-4-iodophenylamino)-N-hydroxy-3,4-difluoro-5-bromobenzamide (PD171984);
2-(2-Methyl-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-bromobenzamide (PD177168);
25 25 2-(2-Methyl-4-iodophenylamino)-N-cyclobutylmethoxy-3,4-difluoro-5-bromobenzamide (PD 180841);
2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-bromobenzamide (PD 184161);
30 30 2-(2-Chloro-4-iodophenylamino)-N-hydroxy-3,4-difluoro-5-bromobenzamide (PD184386);

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2-(2-Chloro-4-iodophenylamino)-N-cyclobutylmethoxy-
3,4-difluorobenzamide (PD 185625);
2-(2-Chloro-4-iodophenylamino)-N-hydroxy-4-fluorobenzamide
(PD 185848);
5 2-(2-Methyl-4-iodophenylamino)-N-hydroxy-
3,4-difluorobenzamide (PD 188563);
2-(2-Methyl-4-iodophenylamino)-N-cyclopropylmethoxy-
3,4,5-trifluorobenzamide (PD 198306); and
2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-
10 4-fluorobenzamide (PD 203311).

15 16. The method of Claim 15 wherein said compound is selected from
2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-
3,4-difluorobenzamide (PD 184352), 2-(2-Methyl-4-iodophenylamino)-N-
cyclopropylmethoxy-3,4,5-trifluorobenzamide (PD 198306); and
2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-
4-fluorobenzamide (PD 203311).

add
AS

- 2-(4-Bromo-2-methyl-phenylamino)-N-(3-dimethylamino-
propyl)-3,4-difluoro-benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-
benzamide;
- 5 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-
ethyl)-benzamide;
- 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyridin-
4-yl-ethyl)-benzamide;
- 10 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(3-hydroxy-
propyl)-benzamide;
- 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyrrolidin-
1-yl-ethyl)-benzamide;
- 15 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenethyl-
benzamide;
- 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-thiophen-
2-yl-ethyl)-benzamide;
- 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-pyridin-
4-ylmethyl-benzamide;
- 20 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-phenethyl-
benzamide;
- 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-piperidin-
1-yl-ethyl)-benzamide;
- 25 5-Chloro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-
2-(4-iodo-2-methyl- phenylamino)- benzamide;
- 5-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-
2-(4-iodo-2-methyl- phenylamino)- benzamide;
- 2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-pyridin-4-yl methyl-
benzamide;
- 30 5-Bromo-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-
2-(4-iodo-2-methyl- phenylamino)- benzamide;
- 5-Chloro-N-(2-diethylamino-ethyl)-2-(4-ido-2-methyl-
phenylamino)- benzamide;